



## Early transition to airway pressure release ventilation may facilitate weaning and improve the outcome of acute respiratory distress syndrome patients.

Adel Taha, MD <sup>(1)</sup>, E-mail: [adeltaha72@hotmail.com](mailto:adeltaha72@hotmail.com),

Amr S. Omar, MD <sup>(2, 3, 4)</sup> E-mail: [a\\_s\\_omar@yahoo.com](mailto:a_s_omar@yahoo.com)

Tamer Elmetwally Farhat <sup>(5)</sup> E-mail: [tamerfarahat2@yahoo.com](mailto:tamerfarahat2@yahoo.com)

Praveen Sivadasan, MD <sup>(3)</sup> E-mail: [drpraveencs@gmail.com](mailto:drpraveencs@gmail.com)

Mohamed Abdelhamid Khalil, MD, PhD E-mail: [mohamedkhalil404@hotmail.com](mailto:mohamedkhalil404@hotmail.com)

- 1) Consultant Intensivist, Critical Care Department, Saqr Hospital, EHS, UAE.
- 2) Professor, Critical Care Department, Beni Suef University Hospital, Egypt.
- 3) Consultant intensivist, heart hospital Hamad medical corporation, Doha, Qatar
- 4) Assistant Professor, Department of Medicine, Weill Cornell Medical College Qatar
- 5) Associate Professor Anesthesia and Intensive Care, Mansoura University Hospital, Egypt.
- 6) Professor of Anesthesia, Cairo university, Egypt. From the Department of critical care medicine/ Saqr Hospital, EHS, United Arab Emirates

### Abstract

**Background:** High mortality is associated with acute respiratory distress syndrome (ARDS).

**Methods:** The study was a retrospective observational study on 39 patients with moderate to severe ARDS admitted between July 2010 and January 2013. Criteria for transition to Airway Pressure Release Ventilation (APRV) included

- failure to wean down FiO<sub>2</sub> below 60% after 24 hours,
- hemodynamic instability due to high positive end-expiratory pressure (PEEP), and
- failure to maintain plateau airway pressure below 30 cm H<sub>2</sub>O.

We compared the outcome of mandatory ventilation (CMV) and APRV groups with particular concern to the duration of mechanical ventilation, the requirement for tracheostomy, the requirement for vasopressors, and survival to ICU discharge.

**Results:** Twenty-four males and 15 females were included in the study with a mean age of 42 years ( $\pm 24$ ). Fourteen out of them fulfilled the criteria and were shifted to APRV within 24 hours of initiating mechanical ventilation. Ten out of 14 (70%) patients in the APRV arm

survived ICU discharge versus 16 out of 25 (64%) patients in the CMV group (p 0.45). Survivors in the APRV group spent significantly shorter periods on mechanical ventilation than survivors in the CMV group (9.6 vs 12.1 days, p 0.03). Furthermore, APRV patients required significantly fewer tracheostomies and less vasopressor.

**Conclusions:**

We concluded that APRV could be effectively used as a rescue mode of ventilation in patients with severe ARDS. Although our study does not show any mortality benefit of using APRV over CMV, there were shorter ventilation days and ICU stay days using APRV.

**Keywords:** APRV, CMV, ARDS

## **Background:**

Acute Respiratory Distress Syndrome (ARDS) is a common condition that is characterized by acute severe hypoxia that is not due to left atrial hypertension. Despite advances in our understanding of the pathophysiology and management of ARDS, it is still associated with high mortality. [1] Maintaining oxygenation and supportive care are the cornerstones of managing ARDS while diagnosing and treating the underlying cause. [2] Airway pressure release ventilation (APRV) was introduced to clinical practice about two decades ago as an alternative mode of mechanical ventilation; however, it had not gained popularity until recently as an effective and safe alternative for difficult-to-oxygenate patients with acute lung injury/ acute respiratory distress syndrome (ALI/ARDS). [3] APRV was described initially by Stock and Downs in 1987 as a continuous positive airway pressure (CPAP) with an intermittent release phase. APRV applies CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or (release time) where most of the ventilation and CO<sub>2</sub> removal occurs. [4]

Using a high-flow (demand valve) CPAP circuit, unrestricted spontaneous breathing can be integrated and can happen any time regardless of the ventilator cycle. If the patient has no spontaneous respiratory effort, APRV becomes typical to 'inverse ratio pressure'-limited, 'time cycle'-assisted mechanical ventilation (pressure-controlled ventilation). [5] Reduction of lung compliance and functional residual capacity (FRC) is associated with ARDS. Therefore, the elastic work of breathing (WOB) is elevated. When CPAP is applied, the FRC is restored, and inspiration commences from a good pressure-volume relationship, assisting spontaneous ventilation and enhancing oxygenation. [6] Applying P high for a T high (80–95% of the cycle time), the mean airway pressure increases, ensuring almost constant lung recruitment (open-lung approach). This is in contrast to the repetitive inflation and deflation of the lung using conventional ventilatory methods, which could result in ventilator-induced lung injury (VILI); or the recruitment manoeuvres, which need to be repeated frequently to avoid de-recruitment. [5, 6]

Minute ventilation and CO<sub>2</sub> removal in APRV depend on lung compliance, airway resistance, the magnitude and duration of pressure release and the magnitude of the patient's spontaneous breathing efforts. Spontaneous breathing plays a very important role in APRV, allowing the patient to control his/ her respiratory frequency without being confined to an

arbitrary preset inspiratory: expiratory ratio (I:E), thus improving patient comfort and patient-ventilator synchrony with reduction of the amount of sedation. Additionally, spontaneous breathing helps drive the inspired gas to the nondependent lung regions by using the patient's own respiratory muscles and through pleural pressure changes without raising the applied airway pressure to a rather dangerous level ( in contrast to conventional mechanical ventilation), thus producing more physiological gas distribution to the nondependent lung regions and improving ventilation/ perfusion (V/Q) matching. [7]

**Objectives:**

To study feasibility and outcome of early transition to APRV as a rescue mode of ventilation for patients with moderate to severe ARDS who failed the initial conventional ventilation.

**Methods:**

Retrospective observational study on 39 patients with severe ARDS who were admitted between July 2011 and January 2013 to Mafraq Hospital ICU, Abu Dhabi, UAE, which is a 20 beds tertiary, multidisciplinary ICU. The diagnosis of severe ARDS was based on Berlin Definition when P/F ratio of less than 200. [8] All patients were managed according to ARDSnet guidelines using low tidal volume CMV (5-7ml/kg). Criteria for transition to APRV included failure to wean down FiO<sub>2</sub> below 60% after 24 hours of the ARDS diagnosis, hemodynamic instability associated with high PEEP, and failure to maintain plateau airway pressure below 30 cm H<sub>2</sub>O. (lower PEEP/ higher FiO<sub>2</sub> table adopted by ARDS net, with PEEP ranging from 5 to 18 cmH<sub>2</sub>O according to FiO<sub>2</sub>).

APRV was provided with a demand valve continuous positive airway pressure circuit of a standard ventilator (Evita XL, Drager Medical AG & Co., Lubeck, Germany). Initial settings of APRV were P high 26 cm H<sub>2</sub>O, P low 2 cm H<sub>2</sub>O, T high 5 seconds, and T low 0.5 seconds with titration of FiO<sub>2</sub> as required, keeping PaO<sub>2</sub> more than 60 mmHg. Manoeuvres to correct poor oxygenation include 1) increasing either 'P high,' 'T high' or both to increase mean airway pressure; 2) changing the patient position to the prone along with APRV. Manoeuvres to correct poor ventilation include:

1. Increase 'P high' and decrease 'T high' simultaneously to increase minute ventilation while keeping stable mean airway pressure
2. Increase 'T low' by 0.05-0.1 s increments
3. Decrease sedation to increase the patient's contribution to minute ventilation

We compared the outcome of CMV and APRV groups with particular concern to the duration of mechanical ventilation, the requirement for tracheostomy, vasopressors requirement and survival to ICU discharge.

The tracheostomy decision was made after ten days when mechanical ventilation is likely to continue. Vasopressors were used to maintain MAP above 65mmHg. We compared the outcome of CMV and APRV groups with particular concern to the duration of mechanical ventilation, the requirement for tracheostomy, vasopressors requirement and survival to ICU discharge.

#### *Statistical analysis:*

The data description was done in the form of the mean (+/-) SD for quantitative data and frequency & proportion for qualitative data. The analysis of the data was done to test the significant statistical difference between groups. For quantitative data, a student t-test was used to compare between 2 groups. For qualitative data chi-square test was used, and an Odds Ratio was detected. [9] Clinical data were entered into a database (Microsoft Excel 2010, Redmond, WA, USA), and statistical analyses were performed (SPSS Inc. version 22 Chicago IL, USA).

#### **Results:**

Twenty four males and 15 females were included in the study with a mean age of 42 years ( $\pm 24$ ), ten patients were screened but met one or more of the exclusion criteria. ). Fourteen out of them fulfilled the criteria and were shifted to APRV within 24 hours of initiating mechanical ventilation (shifting to APRV was based on institution protocol). The most common predisposing factors for ARDS development in our study was community-acquired pneumonia, followed by ventilator-associated pneumonia, H1N1, and transfusion-related acute lung injury (TRALI). There were no statistically significant differences regarding the aetiology between APRV and CMV groups (Table 1). Both groups were matched regarding age, gender, mean APACHE II score on admission, and P/F ratio (Table 1).

Both groups were equally exposed to adjuvant therapy, including *inhaled nitric oxide*, prone ventilation, steroid exposure, neuromuscular blockers, and continuous renal replacement therapy (CRRT). We also noted less sedation requirement in the APRV group, but it did not reach a statistical significance. (Table 2).

Ten out of 14 (70%) patients in the APRV arm survived ICU discharge versus 16 out of 25 (64%) patients in the CMV group; however, this difference did not reach a statistical significance ( $p$  0.45). Survivors in the APRV group spent significantly shorter periods on mechanical ventilation compared to survivors in the CMV group (9.6 vs 12.1 days  $p$  0.03), while 8 out of 16 (50%) survivors in CMV required tracheostomy for prolonged intubation, only 2 out of 10 (20%) survivors in APRV group required tracheostomy tube placement ( $p$  0.02). Eighteen out of 25 patients (72%) required Vasopressors at - some point of time during their ICU stay with total Vasopressors days of 139 days (5.56 days/patient), while only 7 out of 14 patients (50%) of APRV patients required Vasopressors with total days of 42 (3 days/patient) ( $p$  0.02) (Table 3).

The outcome parameters in both groups are described in table (3). Survivors in the APRV group spent significantly shorter periods on mechanical ventilation and ICU than the other group. The mortality in the APRV group was lower than the other group, but it did not reach a statistical significance). The changes in blood gases were compared in both groups- we noted better oxygenation in the APRV group late in the course (Table 4).

### **Discussion:**

In the clinical setting -of ARDS, this study was designed to evaluate the feasibility and outcome of early transition to APRV as a rescue mode of ventilation for patients with moderate to severe ARDS who failed the initial conventional ventilation. Our work did not reveal a statistically significant benefit for APRV over CMV; however, the APRV group of patients had shorter mechanical ventilation days, fewer days in the ICU, and less requirement for vasopressors and tracheostomy.

Acute respiratory distress syndrome (ALI/ARDS) is a common cause of morbidity and mortality in modern ICU, with significant public health implications<sup>9</sup>. Improvements in critical care practice, including mechanical ventilation strategies, have decreased short-term mortality rates for RDS patients. [10] The ARDS Network has demonstrated that a low tidal volume ventilation protocol significantly reduced short-term mortality for RDS patients. [11, 12] Kallet et al. [13] demonstrated that this protocol could be successfully implemented in clinical practice with improved hospital mortality than historical controls. Although some have argued that adopting the exact ARDS Network protocol may be unnecessary, the existing evidence supports that clinicians should change their practice and adopt lung-protective ventilation for patients with ARDS. [14]. However, no studies have

shown that APRV is harmful or significantly inferior to conventional mechanical ventilation.

In this study, it seems that the improvement in gas exchange in the APRV group was mainly caused by the ability of lung recruitment to reduce the amount of collapsed tissue. Previous animal studies support our observation. [15, 16] Wrigge et al., [8] have shown that 4 hours of APRV with spontaneous ventilation resulted in improved oxygenation, higher end-expiratory lung volume, and less non-aerated tissue in diaphragmatic slices compared with APRV without spontaneous ventilation. More recent data suggests that rather than over distending alveoli, the extended T<sub>High</sub>/P<sub>High</sub> redistributes gas from the alveolar ducts to the alveoli, where it belongs [17, 18] and changes heterogeneous to homogeneous alveolar ventilation. [19]

The utilization of sedatives and narcotic analgesics in both groups did not show any statistically significant difference. Walkey et al. compared APRV and CMV in trauma patients ventilated more than 48 hours and found no difference in the sedation requirements between both groups. [20]

In our series, significantly fewer patients required vasopressors in the APRV arm compared with those in CMV. Our results came in agreement with those of Kaplan et al., [21], who demonstrated that APRV increases cardiac performance with decreased pressor use and decreased airway pressure in patients with ARDS. Similarly, Putensen et al. [22], in a comparison study of APRV vs pressure-controlled ventilation in a group of 30 patients, demonstrated Better hemodynamics, fewer intensive care unit days, better oxygenation, less sedation, and lower pressures with APRV. Hering et al. compared APRV with spontaneous breathing (at least 30% of the total minute ventilation) vs APRV with no spontaneous breathing in 12 patients with ALI. This study showed higher renal blood flow, glomerular filtration, and osmolar clearance in the APRV-with-spontaneous-breathing group. [23]

One recent animal study by Roy et al. [24] demonstrates that ARDS can be prevented when APRV is used early in the course of mechanical ventilation in a clinically relevant translational porcine model of lung injury. APRV prevented clinical and histological lung injury by preserving alveolar epithelial integrity, reducing lung edema, preserving surfactant, and maintaining alveolar stability

Andrews et al. [25] conducted a systematic review of observational data in trauma cases which compared the outcome of patients who received conventional ventilation in other centres with those treated with early airway pressure release ventilation in their centre. They observed that early airway pressure release ventilation compared to the other trauma centres represented lower mean adult respiratory distress syndrome incidence and in-hospital mortality. Nevertheless, this study had numerous limitations. To date, none of the trials has been able to demonstrate a mortality advantage by using APRV mode [26]. The major concern with the use of APRV is the overstretching of lung parenchyma and associated loss of lung-protective effect. [27].

**Limitations:**

1. The findings from this survey is limited by the relatively small sample size from a single hospital site, so further validation as part of a large multicentered study is needed.
2. Crossover study – Patients with high ventilator settings (higher PEEP, high plateau pressure ) and poor oxygenation were enrolled in the APRV group at 24 hours – Denoting a more severe form of the disease. Elimination of this confounding factor probably could have resulted in a much better outcome in the APRV group than what was observed in our study
3. Imbalance in the sample size between two groups

**Conclusions:**

We concluded that APRV could be effectively used as a rescue measure of ventilation in patients with moderate to severe ARDS. Although our study does not show any mortality benefit of using APRV over CMV, there were shorter ventilation days and ICU stay days using APRV. Currently, we do not recommend APRV for every patient with ARDS; however, for carefully selected patients, with no apparent contraindications, early application of APRV may be necessary.

However, no studies have shown that APRV is harmful or significantly inferior to conventional mechanical ventilation. There is a need for extensive human trials to compare APRV to conventional mechanical ventilation using lung-protective strategies before concluding this exciting ventilation mode.



**Abbreviation list:**

- ALI Acute Lung Injury.  
APRV Airway Pressure Release Ventilation.  
ARDS Acute Respiratory Distress Syndrome.  
CMV Controlled Mandatory Ventilation.  
CO<sub>2</sub> Carbon Dioxide.  
CPAP Continuous Positive Airway Pressure.  
CXR Chest X Ray.  
FiO<sub>2</sub> Fraction of inspired Oxygen.  
FRC Functional Residual Capacity.  
H<sub>2</sub>O Water.  
I:E Inspiratory : Expiratory Ratio.  
ICU Intensive Care Unit.  
P/F Partial Oxygen pressure/ Fraction of inspired Oxygen.  
PEEP Positive End Expiratory Pressure.  
TRALI Transfusion Related Acute Lung Injury.  
UAE United Arab Emirates.  
V/Q Ventilation/ Perfusion Ratio.  
VILI Ventilator-Induced Lung Injury.  
WOB Work Of Breathing.

**Competing interests:**

The authors declare that they have no competing interests.

**Author's contributions:**

AT did the study design, shared in data collection, and performed the statistical analysis. AS, shared in data collection and helped in writing the manuscript, TE, writing, revision, data analysis PS final revision, writing, MK critical revision, writing. All authors approved the final version

**Key messages:**

1. APRV can be effectively and safely used as a rescue ventilatory method for patients with severe ARDS.
2. APRV, as an effective recruitment maneuver, resulted in better oxygenation and less Oxygen requirement.
3. Patients on APRV had less sedation requirement and better ventilator synchrony.
4. Patients on APRV required fewer tracheostomies and less vasopressors than those on CMV.
5. Although APRV application did not significantly change mortality, yet, it reduced the ventilation days and length of ICU stay.

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	APRV group 14	CMV group 25	P-value
<b>Age</b>	43±24	41.4±22	0.8
<b>Gender (male)</b>	9 (64.2)	15 (60)	0.7
<b>Apache II score</b>	29±8.1	26±6.9	0.8
<b>P/F ratio</b>	133±84	167±96	0.05
<b>Precipitating factor</b>			
<b>CAP</b>	5	9	0.4
<b>VAP</b>	4	7	
<b>H1N1</b>	3	5	
<b>TRALI</b>	2	2	
<b>Not identified</b>		1	
APRV airway pressure release ventilation, CMV controlled mandatory ventilation, CAP community acquired pneumonia, VAP ventilator associated pneumonia, TRALI transfusion related acute lung injury			

Table (1): Demographic characters on admission in both studied groups

	APRV group Number (%) 14	CMV group Number (%) 25	P-value
<b>Prone</b>	5 (35.7)	9 (36)	0.330
<b>Steroid exposure</b>	7 (50)	12 (48)	0.17
<b>Neuromuscular blockade</b>	10 (71.4)	22 (88)	0.04*
<b>Inotropes and vasopressors</b>	7 (50)	16 (64)	0.05
<b>CRRT</b>	3 (21.4)	5 (20)	0.44
<b>Sedation requirements median (IQR)/ventilator day</b>			
Benzodiazepine (mg)	3.1 (0.63–17.4)	4.3 (0.85–19)	0.08
Propofol (mg)	1092 (201–1878)	1240 (206–2257)	0.09
Narcotics (mg)	2.0 (1.1–3.4)	2.4 (1.2–3.9)	0.5
APRV airway pressure release ventilation, CMV controlled mandatory ventilation, iNO – inhaled nitric oxide, CRRT – continuous renal replacement therapy			
NB: Benzodiazepines were calculated in mg for (lorazepam-equivalents), Narcotics were calculated in mg (morphine-equivalents)			

Table (2) Utilization of Adjunct therapies/supportive therapies in both groups

\*Statistically significant ( $p < 0.05$ ).

	APRV group Number (%) 14	CMV group Number (%) 25	P-value
<b>LOS<sub>ICU</sub> median (hours)</b>	269 ± 143	294 ± 191	0.05
<b>LOS<sub>hosp</sub> median (days)</b>	21.6 ± 12.7	28.3 ± 21	0.05
<b>LOV median (hours)</b>	160 ± 97	196 ± 125	0.04
<b>Tracheostomy</b>	4 (28.5)	12 (48)	0.01
<b>Mortality</b>	10 (71)	20 (80)	0.7
APRV airway pressure release ventilation, CMV controlled mandatory ventilation, LOS <sub>ICU</sub> length of stay in intensive care unit, LOS <sub>hosp</sub> hospital length of stay, LOV length of mechanical ventilation			

Table (3) Outcome in both studied groups

Days	Parameters	CMV	APRV	P
<b>Bassline</b>	P/F ratio	105	98	0.08
	PaCO <sub>2</sub>	54	52	0.6
<b>Day 1</b>	P/F ratio	114	143	0.09
	PaCO <sub>2</sub>	52	63	0.7
<b>Day 3</b>	P/F ratio	136	178	0.05
	PaCO <sub>2</sub>	49	55	0.09
<b>Day 7</b>	P/F ratio	143	225	0.04
	PaCO <sub>2</sub>	47	49	0.6

Table (4) Changes in blood gases in both groups